CASE RECORDS

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A 69-year-old woman with hemoptysis, bilateral alveolar infiltrates, and microscopic hematuria

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PRESENTATION OF CASE

History. A 69-year-old woman presented to the emergency department with shortness of breath. Her symptoms began one week prior to admission and were associated with fatigue, malaise, and subjective fever. Two days prior to admission she developed a cough, with one episode of scant hemoptysis. She denied chest pain, purulent sputum production, prior constitutional symptoms, contact with persons with known tuberculosis or other illness, or foreign travel. She kept no pets.

She had a medical history of atrial fibrillation, for which she was treated with digoxin and warfarin, and hypothyroidism, for which she was treated with levothyroxine. She had previously worked as a sales clerk in a retail store, but was retired. She smoked one pack of cigarettes per day from age 21 to age 59, at which time she quit. She did not use alcohol.

Table 1. Hematologic and Chemistry Values

Hematocrit	23.8%
Mean Corpuscular Volume	91 fl
White Cell Count	11,200/mm^3
Neutrophils	78%
Band forms	11%
Lymphocytes	10%
Monocytes	1%
Platelet Count	293,000/mm^3
Serum Sodium	133 mg/dl
Serum Potassium	3.6 mg/dl
Serum Chloride	100 mg/dl
Serum Bicarbonate	18 mg/dl
Blood Urea Nitrogen	57 mg/dl
Serum Creatinine	5.7 mg/dl
Serum Glucose	121 mg/dl

Physical examination. The patient was afebrile, the pulse was 60, respirations were 16, and the blood pressure was 160/100 mm Hg. The conjunctiva were pale. No cervical or supraclavicular adenopathy was present. The rhythm of the heart was irregular, but no other abnormality was present. Inspiratory crackles were present in the mid portions of both lungs on auscultation. No expiratory wheezing was heard. The remainder of the examination was normal.

A sample of arterial blood, while the patient was breathing room air, yielded a pH of 7.38, a pCO_2 of 30, and a pO_2 of 47. The urine was cloudy and red, with an estimated protein content by dipstick of >300 mg/dl. On microscopic examination, the white and red blood cells were too numerous to count, and no casts or crystals were noted. The erythrocyte sedimentation rate was 65 mm/hr. The total serum protein was 6.3 gm/dl, with an albumin fraction which was low at 3.1 gm/dl. Serum transaminases, lactate dehydrogenase, and bilirubin levels were all normal. Other serum

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chemistries and hematologic values are shown in **Table 1**.

A chest x-ray **(Figure 1)** showed bilateral alveolar opacities in a peri-hilar distribution with sparing of the apices and lower lobes. Further laboratory testing and a diagnostic procedure were performed.

Differential Diagnosis

Our patient is a 69-year-old woman who presented with a subacute illness characterized by pulmonary and renal dysfunction. Of note, she did not appear severely ill at presentation. Based on the appearance of her chest x-ray, I will assume that she deteriorated more rapidly following admission. This patient has a disorder which predominantly affects two systems — the lungs and kidneys. I presume that she has a history of long-standing hypothyroidism since she was treated with thyroid replacement therapy. I do not believe that the present illness is directly related to the thyroid disease. One should note that severe hypothyroidism has been associated with mild elevations in serum creatinine levels secondary to increased creatinine production;[1] however, the increase in serum creatinine concentration caused by hypothyroidism does not reach the levels seen in this patient, and hypothyroidism does not affect blood urea nitrogen (BUN) or produce hematuria. Therefore, I will exclude the history of thyroid disease from my consideration of the pulmonary and renal disease.

The patient's pulmonary disease is characterized by dyspnea, hypoxemia, and diffuse alveolar infiltrates that have the appearance of coalescing indistinct nodules without cavitation. She had crackles on auscultation of the chest and possibly some hemoptysis, although this occurred while the patient's anticoagulation therapy was supertherapeutic. Reports of purulent sputum, wheezing, and extra cardiac sounds were notably absent. The arterial blood gas analysis revealed a widened alveolar-arterial oxygen gradient.

The terminology used to describe chest x-ray abnormalities can be quite misleading when used imprecisely. There are four patterns of pulmonary parenchymal involvement: alveolar, interstitial, vascular, and destructive. Destructive implies bullae, cavities, and focal scarring with the honeycomb pattern seen in the end stage. Vascular patterns refer to the normal vascular and lymphatic structures within the thorax, the bronchovascular bundles, the lymphatics, or the lymph nodes.

The remaining two terms, interstitial and alveolar, are most often misused by non-radiologists. These patterns can best be understood by considering the normal lung anatomy. The secondary lung lobule includes all airways distal to the lobular bronchus which includes several acini. The acinus ,or primary lung lobule, is the lung unit distal to the terminal bronchiole and includes respiratory bronchioles with alveolar outpouchings, alveolar ducts, and the terminal alveolar sacs. Theses acini are three to five mm in diameter and are separated from each other by very thin septae, which in normal lungs are below the resolution of the x-ray beam. In x-rays of normal lungs, each air-filled acinus appears black. The surrounding connective tissue is too thin to be seen on chest x-rays. Thus, the x-ray pattern of a normal lung is a black background with linear white structures rep-

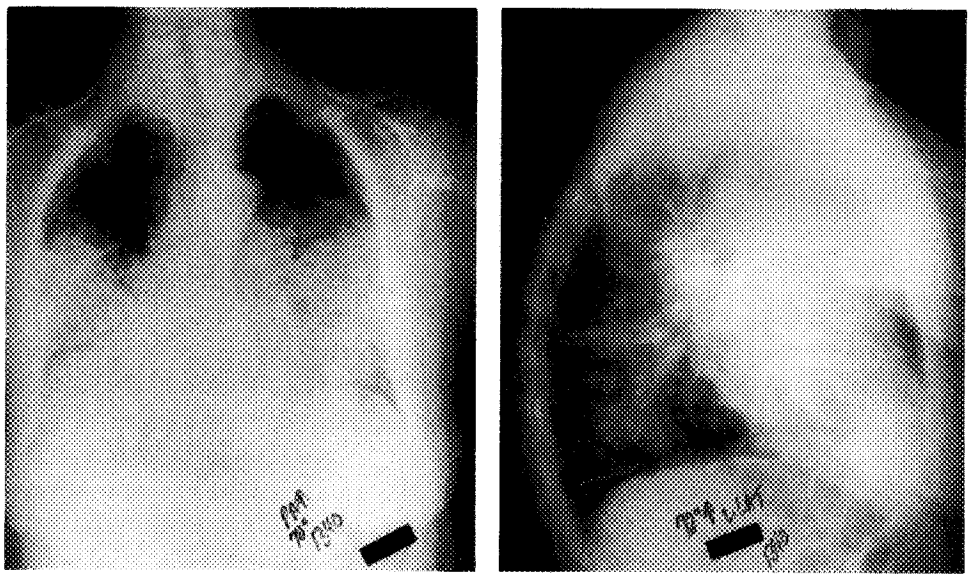

Figure 1a & 1b. PA chest X-ray demonstrating peri-hilar opacities with sparing of the apices and bases.

resenting vascular structures, bronchovascular bundles, pulmonary veins, lymph nodes and fissure planes. If the septae surrounding each acinus are thickened because of fluid, collagen, or inflammation, the x-ray can discriminate distinct air-filled black circles separated from each other by white lines. This produces a lacework pattern termed an interstitial pattern, also called a reticular or periacinar pattern. Interstitial patterns may blur slightly, but do not usually obliterate margins of adjacent structures. If the terminal airways themselves are filled with fluid, inflammatory cells, or cellular debris, or are collapsed, the chest x-ray will appear as a coalescence of white circles. Depending on the pathophysiologic process, these white densities can fill a lobe or an entire lung. They may be patchy or nodular, or appear as large coalescing nodules. In contrast with the interstitial pattern, alveolar processes cause the loss of borders of adjacent structures, the so-called silhouette sign. In the honeycomb lung, or the end-stage destroyed lung, there is thickened connective tissue around the air-filled lung units as seen in the interstitial pattern, but the lung units are much larger and often distorted, either by overdistension or destruction of septae between smaller lung units or by traction secondary to fibrosis.

Our patient's admission chest x-ray shows an alveolar pattern that appears to be a coalescence of many indistinct nodules. The borders of the mediastinal structures are lost and there is a central distribution of the infiltrates. I would classify these changes as an alveolar filling pattern. There is no sign of cavitation, pleural effusion, or pneumothorax.

The renal involvement in our patient is characterized by elevation in both creatinine and BUN, microscopic hematuria, and marked proteinuria, which I will assume is of recent onset. Even with an absence of detectable cellular casts in the urine, this constellation of findings suggests a destructive renal process, involving at least the glomeruli and perhaps other parts of the nephrons. The elevated blood pressure and the low sodium may be additional nonspecific signs of renal disease.

The patient has a low hematocrit. The normal lactate dehydrogenase suggests that the anemia is not caused by ongoing hemolysis. If the renal disease were chronic, it could certainly cause this degree of anemia, but I am assuming the renal disease is new. There is nothing from the history to suggest gastrointestinal blood loss, but there is a persistent loss of erythrocytes in the urine. Furthermore, as we will discuss, the patient may have sequestered blood in the extravascular pulmonary parenchyma. One must also consider if the low hematocrit is part of a systemic disease which also involves the bone marrow; however, the normal platelet count makes this explanation less likely. The patient has some nonspecific findings of ongoing systemic inflammation, as evidenced by a mild leukocytosis, with an elevated percentage of band forms and a high erythrocyte sedimentation rate. Pertinent negative data include a lack of eosinophilia, which will exclude at least one possible diagnosis, and normal serum transaminase levels, which effectively excludes significant acute hepatocellular injury.

Diffuse alveolar hemorrhage usually presents with abrupt onset of dyspnea, hypoxemia, and an alveolar-filling pattern on chest x-ray. Hemoptysis may be mild or absent, since the source of bleeding is the distal airway and blood can be sequestered in the terminal air spaces rather than being cleared to the central airways and expectorated. If the source of the hemorrhage in this patient were the more proximal airways, the hemoptysis should have been more severe.

Alveolar hemorrhage is usually suggested by the clinical and roentgenographic picture. Further evidence of alveolar hemorrhage is provided by one or more of the following procedures. Open lung biopsy or transbronchial biopsy will show an accumulation of erythrocytes and (if the hemorrhage is $\geq$ 2 days old) hemosiderin-laden alveolar macrophages. Bronchoalveolar lavage will also show erythrocytes and hemosiderin-laden alveolar macrophages. Repeated measurement of pulmonary diffusion capacity (diffusing capacity for carbon monoxide or DLCO) can also provide clues to the presence of alveolar hemorrhage.[2] This test measures the absorption of carbon monoxide (CO) during a held breath. The large mass of extravascular blood in alveolar hemorrhage serves as a sink for

CO, increasing the measured DLCO. Because the blood is not circulating, its CO binding sites are saturated and will not be available for binding CO in subsequent DLCO maneuvers. A pattern of an elevated DLCO value, which progressively diminishes with repeated measurements, suggests the presence of extravascular pulmonary blood. Finally, the use of magnetic resonance imaging has been reported to aid in the diagnosis of alveolar hemorrhage, but this technique is not yet widely used for this diagnosis.

This case nicely demonstrates the importance of identifying the key constellation of signs, symptoms, and laboratory data on which to base the differential diagnosis. Failure to do so will result in either a differential diagnosis so broad as to be worthless or to omit the correct diagnosis. The differential diagnosis of oxygenation failure with the chest x-ray changes seen in our patient is very long. Therefore, we have to add some of the key features of this case to allow us to develop a more focused differential diagnosis. I believe the key elements of this case are its subacute nature, the diffuse pulmonary infiltrates and hypoxemia, the renal failure, microscopic hematuria and proteinuria, and the signs of systemic inflammation. In combining these factors, we can reduce the possible diagnoses to a handful of candidates.

I would like to first address and dismiss infectious etiologies. In the absence of sepsis or an adverse effect from antibiotic therapy, bacterial and viral pneumonias do not cause renal failure, with the exception of *Legionella pneumophila* infections.[3] Infection with this pathogen also characteristically causes low plasma sodium levels, as was seen in our patient. Legionella can cause microscopic hematuria, proteinuria and renal failure; however, the patients in whom this is reported are usually very ill at presentation, unlike our patient. Moreover, patients with Legionella infections are rarely afebrile and usually have a productive cough. Thus, Legionella pneumonitis would be an unlikely explanation of our patient's presentation.

Table 2. Causes of pulmonary-renal syndromes

- Goodpasture's syndrome
- Wegener's granulomatosis
- Pulmonary capillaritis
- Polyarteritis nodosa
- Polyangiitis overlap syndrome
- Pauci-immune crescentic glomerulonephritis
- Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
- Mixed cryoglobulinemia
- Henoch-Schonlein purpura
- Hypersensitivity vasculitis

A paraneoplastic syndrome, including nephrotic syndrome, has been reported, albeit rarely, in bronchogenic adenocarcinoma[4] and is believed to be caused by immune complexes containing tumor antigens. Thus, adenocarcinoma of the lung with widespread pulmonary metastasis could explain the patient's pulmonary and renal disease, but the acute onset of the respiratory symptoms does not favor this diagnosis. Bronchoalveolar cell carcinoma, which would be more consistent with the chest x-ray appearance, has not been identified with this paraneoplastic lesion as far as I know. Alternatively, renal cell carcinoma, with locally advanced disease causing renal failure, could metastasize to lung and spread via the airway route to cause a chest x-ray pattern similar to our patient's x-ray, but again this scenario is quite unlikely.

I believe this patient has an immunologic disorder causing her pulmonary and renal disease. I will discuss these possible diagnoses (**Table 2**) and see how they fit the available clinical and laboratory data.

Goodpasture first described a syndrome of diffuse alveolar hemorrhage and glomerulonephritis in 1919 in an 18-year-old man who died 6 weeks after a presumed bout of influenza.[5] Today, we realize that the active factor is an autoantibody targeted against glomerular and alveolar basement membrane.[6] Patients, usually men between 20 and 40 years old, present with acute or subacute onset of cough, dyspnea, and hemoptysis. The disease occurs with equal frequency in older men and women. Renal and pulmonary disease are discovered coincidentally in 60% to 80% of the cases, but most of the patients who present with alveolar hemorrhage are current cigarette smokers. Our patient was not actively smoking. Demonstrating circulating anti-glomerular basement membrane (GBM) antibodies in the correct clinical setting is diagnostic for this disease,[7] but results may take several days to be reported. Renal biopsy demonstrating linear immunoglobulin deposits along the glomerular basement membrane can provide the diagnosis more rapidly. Treatment of Goodpasture's disease consists of corticosteroids, cytotoxic agents,

and plasmapheresis. Two-year survival is only 50%, with most deaths caused by diffuse alveolar hemorrhage or infection.[8] Our patient is a bit old for this diagnosis, but otherwise a good fit.

Idiopathic pulmonary hemosiderosis is a disease of children, with only 20% of cases occurring in adults. In fact, the oldest reported patient with this disease was 62 years of age,[9] 7 years younger than our patient. The disease usually presents as a progressive respiratory failure, abnormal chest x-ray, and iron-deficiency anemia. Renal involvement is rare and, for some clinicians, would exclude this diagnosis. The etiology is unknown, but histopathologic exam shows alveolar wall necrosis, intra-alveolar blood, hemosiderin-laden macrophages, immune complex deposition, and interstitial fibrosis. Treatment consists of immunosuppressive therapy and blood transfusions. In children, mean survival is three to five years, but mortality is much lower in adults with this disease. Our patient's age and her renal involvement make this diagnosis very unlikely.

Polyarteritis nodosa is a multisystem disease characterized by a necrotizing vasculitis of the small and medium size arteries in multiple organs, including kidney, liver, nervous system, skin, and joints, but rarely in the lungs.[10] In fact, those cases of polyarteritis nodosa with lung involvement are probably misdiagnosed cases of Churg-Strauss angiitis[11] or the so-called polyangiitis overlap syndrome.[12] Thus, I will dismiss this diagnosis in our patient, in whom lung involvement is a major feature.

Anaphylactoid purpura or Henoch-Schonlein purpura (HSP) is a form of leukocytoclastic immune complex vasculitis characterized by the triad of purpura, arthritis, and abdominal pain. It is predominantly seen in children, but can also occur in adults.[13] Glomerulonephritis and renal failure can occur, but respiratory involvement is rare. Our adult patient had none of the usual presenting signs and symptoms of HSP. So, I will dismiss this diagnosis as well.

A family of vasculitides characterized by granuloma formation are the most common type of pulmonary vasculitis. Of these, Wegener's granulomatosis is the most common diagnosis. Originally described by Wegener in 1939 as a necrotizing granulomatous vasculitis of the upper and lower respiratory tract and glomerulonephritis,[14] it is now seen in variable clinical presentations,[15] including limited Wegener's granulomatosis involving only the lower respiratory tract.[16] Wegener's granulomatosis presents most commonly in middle age, with systemic symptoms and either upper or lower respiratory symptoms, including cough, dyspnea, and hemoptysis. The onset is variable, ranging from insidious to abrupt. Pulmonary involvement is characterized as infiltrates in 63% of cases, multiple nodules simulating metastatic disease in 31%, and with cavitation in only 8% to 10% of cases.[17,18] Upper airway involvement is a feature in 80% of cases of Wegener's, but occurs in less than half of patients in whom Wegener's granulomatosis presents as alveolar hemorrhage,[19] which I believe occurred in our patient. Renal failure is seen in 15% of patients initially presenting with Wegener's. Diagnosis is based on the clinical presentation and open lung biopsy showing parenchymal necrosis, granulomatous inflammation and inflammatory cell infiltration with neutrophils, lymphocytes, plasma cells, and eosinophils. Blood vessel obstruction and infarcts occur in one-third of cases with an accompanying capillaritis and alveolar hemorrhage.[20] Unlike Goodpasture's disease, the renal pathologic findings in Wegener's granulomatosis are not sufficiently specific to be diagnostic. Demonstration of anti-neutrophil cytoplasmic antibodies (ANCA) of the "C" or cytoplasmic type, which are targeted against protease III, further supports the diagnosis. "P" or perinuclear ANCA are targeted to anti-myeloperoxidase and other cell proteins and are more commonly seen in non-Wegener's vasculitides in which capillaritis is more prominent.[21] The etiology of this class of vasculitides is unknown, but the ANCA itself may contribute to the disease activity by activating neutrophils.[22] Wegener's granulomatosis represents one of the great successes in treating immunologic disorders. Before the onset of therapy, the disease was uniformly fatal with survival of only a few months. With present therapy, corticosteroids and cyclophosphamide, complete remission is achieved in 75% to 90% of patients.[19]

Churg-Strauss syndrome, also called allergic granulomatosis and angiitis, was described in 1951 in a series of 13 patients presenting

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with severe asthma associated with fever and hypereosinophilia.[11] Granulomatous vasculitis can affect small arteries in many organs, including lungs, peripheral nerves, skin, and heart, but it uncommonly involves the kidneys.[23] Our patient's lack of eosinophilia and wheezing and the low incidence of renal involvement with this disease make this diagnosis unlikely.

Lymphomatoid granulomatosis was described in 1972 by Liebow and colleagues as a unique form of pulmonary angiitis characterized by an angiocentric and angiodestructive infiltration of the upper and lower respiratory tract, skin, central nervous system, and uncommonly the kidneys.[24] Chest x-ray abnormalities were indistinguishable from those in patients with Wegener's granulomatosis. T cells predominate in the cellular infiltrates, and lymphomas either predate or subsequently develop in many of these patients.[25] Remission is induced in half of the patients with immunosuppressive therapy. Lymphoma develops in most of the other patients. Because this disease rarely affects the kidneys, I will not consider this diagnosis further in our patient.

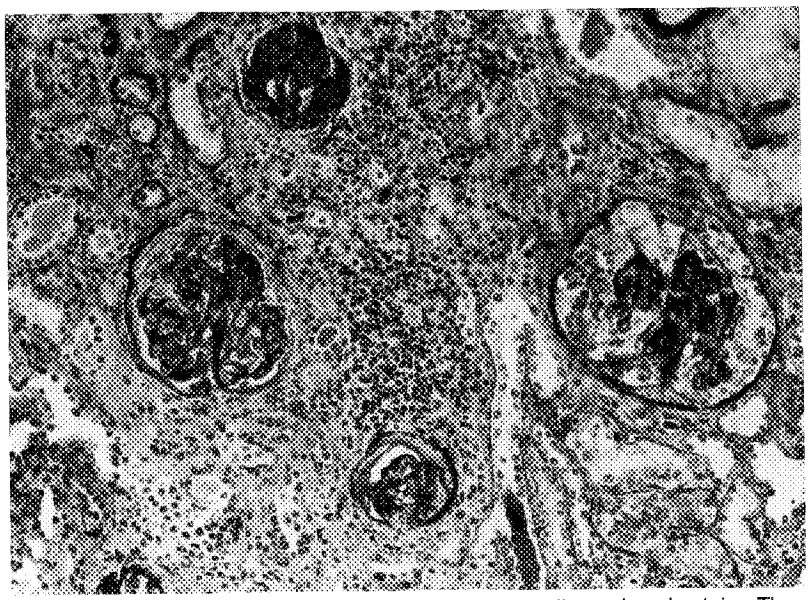

Figure 2. Light microscopy of kidney biopsy, hematoxylin, and eosin stain. The section shows four glomeruli in various stages of crescent formation, crowding of glomerular tufts, necrosis and sclerosis.

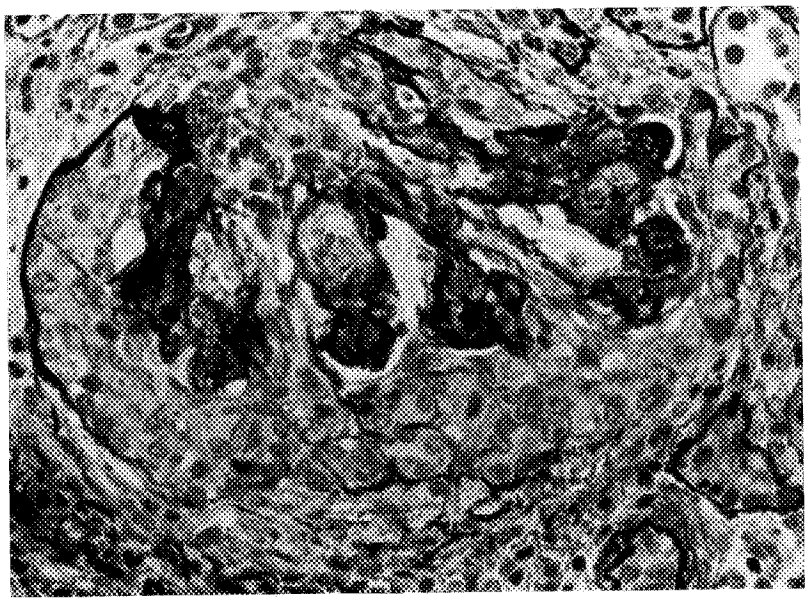

Figure 3. High power view of a glomerulus with well-developed epithelial crescent.

Liebow also described a probable variant of sarcoidosis which he termed necrotizing sarcoid granulomatosis.[26] This syndrome is characterized by confluent granulomas, similar to those seen in sarcoidosis, associated with minimally necrotic granulomatous vasculitis of the pulmonary vessels, pulmonary nodules, or infiltrates, without hilar adenopathy. Patients with this syndrome usually have a benign course. Renal involvement, when it occurs, is usually characterized by an interstitial nephritis and renal tubular acidosis. Renal failure in sarcoidosis is usually caused by extensive nephrolithiasis caused by increased serum calcium levels. The calcium level in our patient was normal. Therefore, I am also discounting this diagnosis.

Acute lupus pneumonitis is an uncommon feature of systemic lupus erythematosus (SLE), which most frequently occurs in younger patients with the disease.[27] Its onset can be acute or subacute and can cause alveolar hemorrhage in 1% to 2% of cases.[28] Histopathologic evaluation shows the typical findings of alveolar hemorrhage with small vessel angiitis, and in half the cases, immune complex deposition can be demonstrated. Alveolar hemorrhage in SLE has a high mortality rate (50% to 75%), with death from respiratory failure, despite treatment with corticosteroids and cytotoxic agents.[28] SLE involves many organ systems, including the kidneys as seen in our patient, but it is uncommon for this disease to initially present as a pneumonitis.

Mixed cryoglobulinemia, a systemic vasculitis caused by the presence of cryoglobulins in the circulation, can involve both kidneys and lung, but it usually includes purpuric skin lesions, hepatitis, and arthritis, none of which were seen in our patient. Furthermore, the lung

involvement in this disease is most often a chronic interstitial process,[29] rather than the subacute alveolar filling process which occurred in our patient. Sjogren's disease can present with both lung and renal involvement, but our patient did not have any symptoms that comprise the sicca complex, dry eyes and mouth. Furthermore, the lung involvement in Sjogren's syndrome is more chronic and interstitial in nature, as seen in mixed cryoglobulinemia. The mucocutaneous ulcerations in Behcet's disease can involve the larger airways and present with alveolar hemorrhage,[30] but our patient is quite old to experience an initial presentation of Behcet's, nor does she demonstrate any of the stigmata of the disease. Moreover, since the source of bleeding in Behcet's is from the more proximal airways, I would have expected more severe hemoptysis if the pulmonary disease was a manifestation of Behcet's disease. I think we can safely exclude these three diagnoses.

I have narrowed down the diagnostic possibilities for this patient's pulmonary-renal syndrome to three: Wegener's granulomatosis, systemic lupus erythematosus; and Goodpasture's disease. Although she lacked the evidence of upper airway involvement which is part of the classic triad of Wegener's, this can be absent in over 50% of cases of Wegener's granulomatosis. The subacute onset of disease can be seen in all three entities, but the age of onset and the nodular x-ray appearance of the pulmonary infiltrates best fit the diagnosis of Wegener's granulomatosis or a related vasculitis.

Clinical diagnosis. I believe the patient had Wegener's granulomatosis or a related pulmonary capillaritis. The positive laboratory test was probably an ANCA measurement, and the open lung biopsy likely showed the features of Wegener's granulomatosis or pulmonary capillaritis.

Pathologic diagnosis

A percutaneous biopsy of the right kidney was performed. Microscopic sections show marked pleomorphic glomerular changes. The various glomerular lesions are dominated and characterized by crescent formation in addition to changes in the glomerular tufts. Many glomeruli show fibro-epithelial crescents with compression of the glomerular tufts **(Figures 2 and 3)**. Although most glomeruli are involved, there are occasional normal glomeruli seen (in a representative section, 20 of 35 glomeruli were globally or segmentally sclerotic). Other glomeruli show focal hypercellularity and fibrinoid necrosis. Tubular changes are seen with vacuolization and tubular sloughing, and there are foci of tubulitis. There is marked interstitial fibrosis and interstitial inflammatory infiltrate by mononuclear and polymorphic nuclear leukocytes, as well as atrophy and tubular dilation. Immunofluorescence microscopy, performed at another laboratory, showed rare foci of C3 and IgG immunoreactivity within crescents and, more rarely, within glomerular segments. Peritubular linear C3 immunoreactivity was present. Fibrinogen immunoreactivity was present within the glomerular crescents and necrotizing foci, tubules, and interstitium. No significant IgA, IgM, or C1q immunoreactivity was noted. The light microscopic findings are consistent with a necrotizing glomerulonephritis with many crescents, and together with the immunofluorescence findings, this is consistent with a pauci-immune necrotizing glomerulonephritis.[31,32,33]

Anti-basement membrane antibodies in serum were reported by the Corning Nichols Institute as being <5 units, which is considered normal. "C" type anti-neutrophilic antibodies were reported at < 7 EU/ml, which is considered normal, but the "P" type ANCA was reported at 27 EU/ml (normal < 7). The pauci-immune pathologic appearance, the presence of ANCA antibodies, and the clinical course suggest either Wegener's granulomatosis or a microscopic polyarteritis. The presence of "P" type ANCA antibodies, and the absence of "C" type antibodies makes the diagnosis of microscopic polyarteritis more likely.

Follow-up

The patient was treated with cyclophosphamide and prednisone, which resulted in rapid and substantial improvement in her pulmonary infiltrates. Her renal function improved, although she continued to exhibit azotemia. Two months later, she developed severe pancytopenia, requiring cessation of cyclophosphamide and treatment with granulocyte colony stimulating factor. Three months after her initial diagnosis, she was admitted with recurrent pulmonary infiltrates, hypoxemia and fever, but refused repeat bronchoscopy, and was treated empirically for possible pneumonia, as well as recrudescence of her underlying illness.

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